Public Workshop— Facilitating Antibacterial Drug Development for Patients With Unmet Need

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Welcome

Public Workshop— Facilitating Antibacterial Drug Development for Patients With Unmet Need

- An opportunity for discussion
- Not an Advisory Committee
- Conflict of Interest disclosures available
- Open time for comments

Panel Introductions

Agenda

	Day 1: Monday July 18th, 2016	
Time	Topic	Presenter
8:30 -10:30 AM	Session 1: General Considerations for Unmet Need Programs	
8:30-8:50	Effectiveness standards including orphan products	Ed Cox
8:50-9:10	Trial Considerations for Unmet need	Sumathi Nambiar
9:10-9:30	Regulatory pathways and approaches to unmet need	Marco Cavaleri
9:30-9:50	Developing antibacterial drugs for unmet need and so that we stay ahead of the epidemic: Points to consider for developers	John Rex
9:50-10:10	Pharmacokinetic considerations in unmet need programs	Paul Ambrose
10:10-10:30	BARDA's market research for a clinical trial network for antibiotics	Joe Larsen
10:30-11:00	Break 1	
11:00-11:30	Clarifying Questions (Panelists and Audience)	

Agenda

11:30-12:10	Session 2: Real World Experiences in Conducting such Trials	
11:30-11:45	Developing antibacterial drugs for patients with unmet need: experience and recommendations	Ian Friedland
11:45-12:00	Planning and Executing a Carbapenem/Beta-lactamase Inhibitor Program Focused on Treatment of KPC-Producing CRE	Mike Dudley
12:00-12:15	Clarifying Questions (Panelists and Audience)	
12:15-1:00	Lunch	
1:00-2:00	Panel Discussion 1	
2:00-3:00	Session 3: Statistical Considerations	
2:00-2:20	Evaluating antibacterial drugs in unmet need settings	Dan Rubin
2:20-2:40	Innovative Trial Designs	Kert Viele
2:40-3:10	Clarifying Questions (Panelists and Audience)	
3:10-3:30	Break 2	
3:30-4:00	Public Comments	
4:00-5:00	Panel Discussion 2 (covering all topics)	

Background

- Antibacterial drug development is challenging from both a scientific and economic standpoint
- Scientific
  - urgent need to initiate therapy in seriously ill patients
  - diagnostic uncertainty
  - pre-study or overlapping antibacterial drug therapy can obscure evaluation of efficacy of an investigational drug
  - mature field with many targets already identified
  - alternatives to small molecule antibacterial drugs generally a less mature field – greater risk/uncertainty
- Economic
  - short course of treatment used episodically
  - prudent use essential -- has economic implications

Antibacterial Drug Development

- Standard Development Programs
  - Other effective therapies are available
  - Provides foundation for evaluating safety and efficacy of a drug
  - Feasible to study the clinical conditions
  - Degree of uncertainty regarding efficacy and safety is limited
- Unmet Need Development Programs
  - Address an existing or future unmet need
  - Molecule has characteristics to address an unmet need
  - Smaller programs, with greater uncertainties in safety and efficacy
  - Reserved for use in patients with limited or no treatment options

Current State

- Fragile antibacterial drug pipeline
- GAIN – Qualifying Infectious Disease Product (QIDP) fast track designation upon request, priority review, 5y of additional exclusivity, for qualifying drugs
- 107 QIDP designations for 63 different unique molecules
- In general, most drugs that enter phase 1 are not ultimately shown to be safe and effective
- A high level of innovation is challenging to achieve in this mature field
- Response involves therapy, immune system, tissue repair

Recent Approvals

- Ceftaroline for CABP and ABSSSI, October 2010
- Fidaxomicin for *C. difficile*-associated diarrhea, May 2011
- Bedaquiline for multidrug-resistant pulmonary tuberculosis (MDRTB), December 2012
- Dalbavancin for ABSSSI, May 2014
- Tedizolid for ABSSSI, June 2014
- Oritavancin for ABSSSI, August 2014
- Ceftolozane-tazobactam for cUTI and cIAI, December 2014
- Ceftazidime-avibactam for cUTI* and cIAI, February 2015

CABP: Community acquired bacterial pneumonia; ABSSSI: Acute Bacterial Skin and Skin Structure Infections
* Reserve for use in patients who have limited or no alternative treatment options.
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Unmet Need

- Emerging resistance and a less than robust antibacterial drug development pipeline have led to unmet need
  - Multidrug-resistant Gram-negative rods
- Ideally, ongoing development provides for new options to address current needs and needs that we anticipate will arise in the years ahead
- Difficult to react in a timely fashion once an unmet need situation has arisen

Unmet Need: Trial Design Options

- Non-inferiority trial in a body site of infection
- Superiority trial in one body site of infection or pooled across body sites
- Nested NI-superiority trial
- For an approved β-lactam being developed with a new β-lactamase inhibitor can rely in part on previous findings of safety and effectiveness
- Superiority of adjunctive therapy plus SOC versus SOC

Non-inferiority Trials – Important Design for Antibacterial Drugs - 1

- Opportunity to show superiority is likely time limited – dependent on standard of care that is less than adequate
- Enrolling patients with infrequently occurring highly resistant phenotypes in a clinical trial is difficult
  - testing the drug -- vs. -- testing the test and testing the drug
  - Drug may “fail” because the test can’t be performed
- Do not want to wait for incidence of highly resistant organisms to be high enough to make superiority trials easy to perform
- “Best available therapy” likely has a treatment effect – “resistance” often not binary a likelihood of response – so can be difficult to show superiority

Non-inferiority Trials – Important Design for Antibacterial Drugs - 2

- Once new standard of care (SOC) demonstrated, ongoing trials will need to incorporate new SOC to remain ethical – superiority hypothesis may become unrealistic
- Drugs that have different mechanisms of action, chemical modifications that are stable to resistance mechanism, or paired w/ resistance inhibitor may have value beyond what is shown in clinical trials
- The existing drugs we rely on were studied against prevailing resistance phenotypes at time of development – some retain activity and are useful for treating resistant organisms that were not prevalent when developed

Superiority Trials

- Provide clear evidence of efficacy
- Can be challenging to conduct
  - details to follow
- Some interested in such claims
- Avoids concerns some may have regarding generalizability
- May wish to balance with a more achievable approach if interested in pursuing superiority with

Disease Characteristics and Trial Designs

- Serious acute bacterial diseases
- Oncologic conditions
- HIV/HCV
- Rare metabolic disorders

  - Identifying patients
  - Disease course over time
  - Diagnostic certainty
  - Urgency to initiate therapy
  - Variability in outcomes and time to clinical outcome
  - Opportunities for rescue therapy for patient not responding

Clinical Trials - Lessons Learned

- Clinical trials continue to teach us important lessons that are often unexpected
  - Daptomycin: CABP didn't meet NI margin; binding to surfactant
  - Doripenem: Higher mortality and lower cure rates in VABP
  - Tigecycline: Higher mortality and lower cure rates in VABP
  - Ceftobiprole: Lower cure rates in VABP
  - Delafloxacin: Monotherapy may not be sufficient to treat some patients with uncomplicated gonorrhea
  - Eravacycline: cUTI didn't meet NI margin; successful trial in cIAI

Silverman. J Infect Dis. 2005
Pertel. Clin Infect Dis 2008;
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm
http://www.fda.gov/drugs/drugsafety/ucm369580.htm
Ambrose Clin Infect Dis 2010; Udy Int J Antimicrob Agents. 2012
Awad et al. Clin Infect Dis 2014
http://www.melinta.com/news.php?c=41
http://ir.tphase.com/releasedetail.cfm?ReleaseID=930613

HABP/VABP Studies – Clinical Trials.gov - 1

- **Recruiting - Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008**)

  Condition:Nosocomial Pneumonia

  Interventions: Drug: ceftolozane/tazobactam; Drug: Meropenem

- **Recruiting - A Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE)**

  Conditions: Bloodstream Infections (BSI) Due to CRE; Hospital-Acquired Bacterial Pneumonia (HABP) Due to CRE; Ventilator-Associated Bacterial Pneumonia (VABP) Due to CRE; Complicated Urinary Tract Infection (cUTI) Due to CRE; Acute Pyelonephritis (AP) Due to CRE

  Interventions: Drug: plazomicin; Drug: colistin; Drug: meropenem; Drug: tigecycline; Drug: antibiotic of Investigator's choice

- **Recruiting - Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014)**

  Condition:Bacterial Pneumonia

  Interventions: Drug: Imipenem; Drug: Relebactam; Drug: Cilastatin; Drug: Piperacillin; Drug: Tazobactam; Drug: Linezolid

HABP/VABP Studies – Clinical Trials.gov - 2

- **Recruiting - Efficacy, Safety, Tolerability of Carbavance Compared to Best Available Therapy in Serious Infections Due to Carbapenem Resistant Enterobacteriaceae, in Adults**

  Conditions: Urinary Tract Infection Complicated;Acute Pyelonephritis; Hospital Acquired Bacterial Pneumonia; Ventilator-associated Bacterial Pneumonia; Bacteremia

  Interventions: Drug: Carbavance; Drug: Best Available Therapy
- **Recruiting - TR-701 FA vs Linezolid for the Treatment of Nosocomial Pneumonia**

  Condition:Pneumonia

  Interventions: Drug: TR-701 FA IV; Drug: Linezolid
- **Recruiting - Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection (MK-7655A-013)**

  Condition:Bacterial Infections

  Interventions: Drug: Imipenem+Cilastatin/Relebactam; Drug: Colistimethate sodium (CMS); Drug: Imipenem+Cilastatin; Drug: Placebo to CMS

Advancing the Science of Clinical Trials

- FNIH – developing & evaluating endpoints
- CTTI – trial efficiency and design
  - HABP/VABP project to make trials more feasible
- Duke Margolis Center – over-arching issues in antibacterial drug development
- EMA and FDA frequent interactions – TATFAR and through our confidentiality agreements
- Curating the science supporting clinical trial design and endpoints is key both here in the U.S. and for harmonizing available approaches internationally

Value of a Multi-Faceted Multi-Stakeholder Approach

- Resistance Surveillance
- Prevention of Infection
- Stewardship
- Research and Development
- Role of
  - Academia
  - Industry
  - Government
  - Hospitals
  - Patients
  - Society
  - Prof. Societies
  - Others
  - Public Pvt Part
  - Payers

Overcoming the Challenges

- Solutions will need to address multiple factors
- Basic science R&D → early development → advanced development
  - Pharmaceutical companies
  - NIAID & BARDA
- ERG report – societal value >> private value
  - incentives / purchasing strategies
    - push and pull

Clinical Trial Network

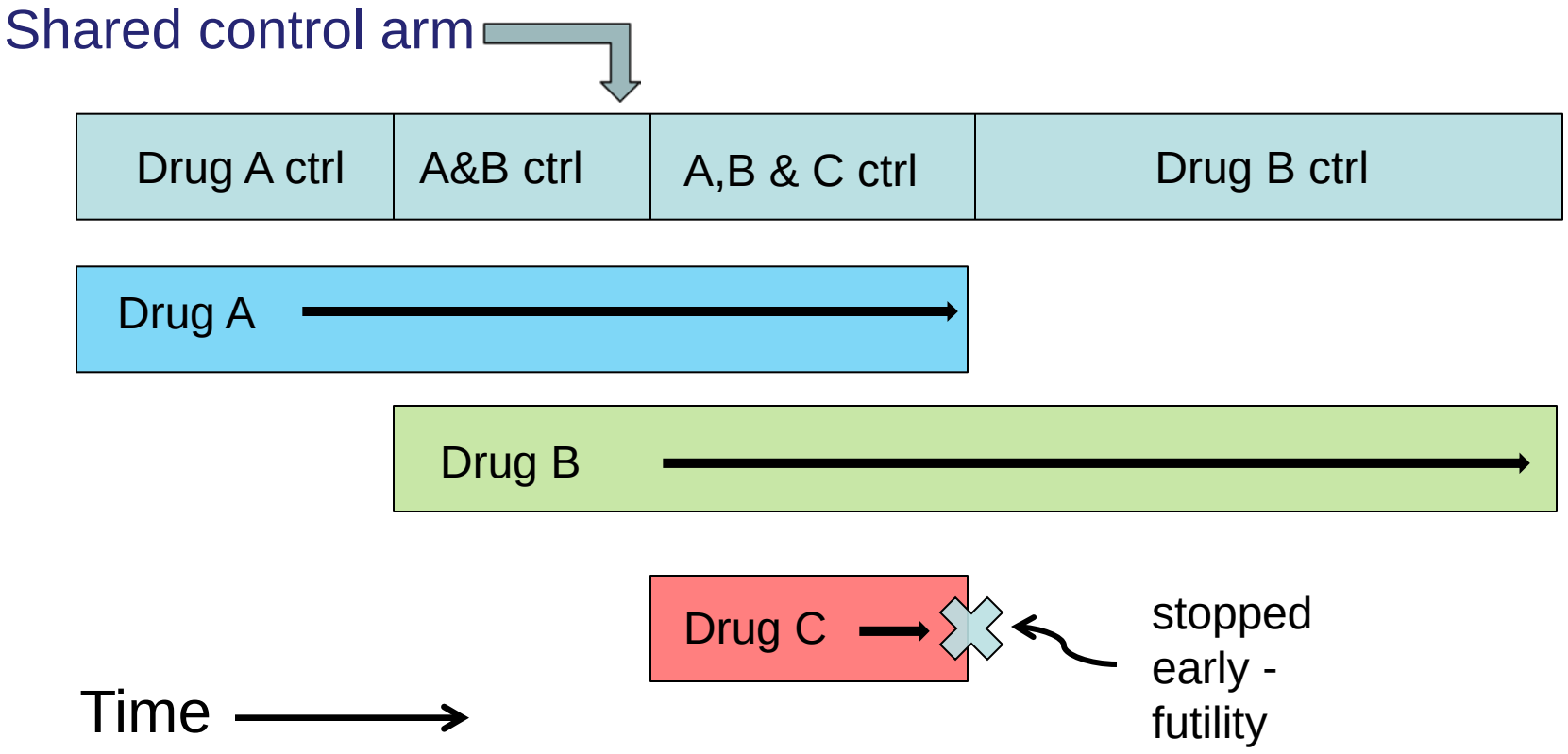
- BARDA Request for Information*
- Clinical trial network for studying antibacterial drugs
  - Infrastructure – avoid starting from scratch each time
  - Expertise – improve quality and conduct
  - Lab support
  - Common protocol
    - Can study more than one drug – share control arm
  - Utility for diagnostic test development

*https://www.fbo.gov/spg/HHS/OOS/OASPHEP/BARDA-RFI-Clinical_Trial_Network_for_Antibacterial_Drugs/listing.html

Master Protocol – Antibacterial Drugs

An example Master Protocol schematic to study several drugs for the treatment of patients with a particular bacterial disease

- Enroll patients with HABP/VABP



Thank you